Clinical Nutrition ESPEN 31 (2019) 17–22

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

Patient-generated subjective global assessment predicts cachexia and death in patients with head, neck and abdominal cancer: A retrospective longitudinal study

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ARTICLE INFO

Article history:
Received 21 February 2019
Accepted 20 March 2019

Keywords:
Cachexia
Malnutrition
Nutritional assessment
PG-SGA
Head and neck cancer
Abdominal cancer

SUMMARY

Background & aims: Cancer is a complex disease, with poor prognosis when associated with malnutrition. This condition can lead to Cancer Cachexia (CC), a syndrome characterized by loss of muscle mass with or without fat loss, often associated with higher risk of death. Although there are recommended screening tools to assess nutritional status in cancer patients, such as Patient-Generated Subjective Global Assessment (PG-SGA), little is known about CC prediction. The aim was to investigate the association between nutritional status of patients with head, neck and abdominal cancer, assessed by PG-SGA at the day of hospitalization, with CC, hospitalization time and death.

Methods: This is a retrospective longitudinal study, where we collected data of 97 patients about PG-SGA nutritional classification, anthropometry, gender, age, cachexia diagnosis and death.

Results: PG-SGA classification was strongly associated with all the anthropometric measures ($p < 0.0001$). According to PG-SGA classification, 30.61% ($n = 15$) of patients in group A developed pre-cachexia; 38.24% in group B developed CC ($n = 13$); and 60% ($n = 9$) in group C developed refractory cachexia ($p < 0.0001$). Death rate was 24.49% ($n = 12$), 54.55% ($n = 18$) and 80% ($n = 12$) in groups A, B and C, respectively ($p < 0.0001$). PG-SGA had good sensibility (89.5%) and accuracy (72%) for CC, and also good specificity (75.51%) and accuracy (69%) for death.

Conclusions: PG-SGA demonstrated a significative association with the variables measured and was able to predict CC and death. This, in addition to its simple applicability, suggests that PG-SGA can be a useful tool to screen cancer patients for CC establishment and death risk.

1. Introduction

Malnutrition prevalence in cancer varies between about 20 and 70% [1]. Diverse effects are associated with malnutrition in cancer patients, such as low quality of life, adverse events due to chemotherapy and/or radiotherapy, poorer prognosis and shorter overall survival [1,2]. The nutritional status exerts a pivotal role in oncologic patients' mortality, with studies estimating that about 20% of the deaths are related to malnutrition and its consequences [3].

Cancer Cachexia (CC) is a syndrome related to malnutrition in cancer patients, developed by both reduced dietary intake and abnormal metabolism [4]. According to Fearon et al. [5], the main

Abbreviations: CC, Cancer Cachexia; PG-SGA, Patient-Generated Subjective Global Assessment; aPG-SGA, Abridged Patient-Generated Subjective Global Assessment; INCA, National Institute of Cancer; BMI, Body Mass Index; TST, Triceps Skinfold Thickness; MAMC, Mid-Arm Muscle Circumference; SD, Standard Deviation; IQR, Interquartile Range; PPV, Positive Predictive Value; NGV, Negative Predictive Value.

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https://doi.org/10.1016/j.clnesp.2019.03.013
2405-4577/

characteristic of CC is muscle mass loss, associated or not with fat loss, that cannot be totally reversed with conventional nutritional therapy. CC may also be associated with anorexia, fatigue, asthenia, inflammation and other metabolic disturbances, which leads to the perpetuation of CC. Since the presence of CC is ultimately related to death and evidence shows an overwhelming prevalence of 50–80% in cancer patients, its screening is essential for better prognosis and survival [1–5].

To identify and diagnose malnutrition, several nutritional screening tools are suggested, based on image, clinical, laboratory, dietary and subjective factors [2,4]. Part of them, unfortunately, are not very accessible, mainly because of the high financial cost associated with the equipments. In this context, tools like the Patient-Generated Subjective Global Assessment (PG-SGA) emerge, since it is a low cost, easy to apply subjective questionnaire with various studies showing the positive effect of PG-SGA in estimating the nutritional status of patients with cancer [6].

PG-SGA classifies individuals according to their nutritional status in A, B and C: well nourished, moderately malnourished and severely malnourished, respectively. The good performance of PG-SGA in malnutrition screening in cancer patients is recognized by several national guidelines for nutrition in oncology worldwide, with countries like United States of America and Brazil recommending its utilization [6].

Regarding CC, few studies investigated the performance of PG-SGA as a screening tool. Ozorio, Barão and Forones (2017) [7] compared PG-SGA, phase angle and handgrip strength in order to classify patients with gastrointestinal cancer according to cachexia stage. They showed that all the three methods were related to CC, with high statistical association. Vigano et al. (2014) [8], on the other hand, tested whether the Abridged Patient-Generated Subjective Global Assessment (aPG-SGA), a variation of the original PG-SGA, could be used for early detection of CC. Their results show that aPG-SGA was significantly associated with biological and anthropometric markers of CC, suggesting it may be a useful tool for CC screening in cancer patients.

To the best of our knowledge, no study investigated whether PG-SGA can predict the onset of CC. Considering the impact of this syndrome in the prognostic of cancer patients, we aimed to investigate the association between nutritional status of patients with head, neck and abdominal cancer, assessed by PG-SGA at the day of hospitalization, with CC, hospitalization time and death.

2. Materials and methods

2.1. Study design and patients

This is a retrospective longitudinal study placed at National Institute of Cancer (INCA, Brazil), a national reference hospital for the treatment of cancer. Patients eligible for the study were adults ($\geq$20 years old), hospitalized in INCA during November 2012 and capable of answering the questions of PG-SGA on their own or with help. Data of the patients were collected from the medical records. Patients with medical records lacking some information needed for this study were excluded. Informed consent was obtained from each of the 97 patients upon recruitment. The project complied with ethical principles and the Declaration of Helsinki. The study was approved by the Research Ethics Committee of INCA under Registration number 34746.

2.2. Nutritional assessment and clinical evaluation

All patients performed a PG-SGA. This questionnaire is divided in two parts: the first one, where the patient answer questions about recent weight loss, dietary intake, gastrointestinal symptoms and functional status, grading scores according to the intensity of the problem listed; and the second one, answered by the health professional who is applying PG-SGA, with questions graded regarding diagnosis, metabolic demand and a physical exam realized on the patient. The sum of all grades leads to a number, which classifies the patient in: 0–1, routine follow-up, with no need of nutritional intervention; 2–3, might benefit from nutritional education; 4–8, requires nutritional intervention by a dietitian; $\geq$9, critical need of a nutritional intervention. Moreover, this result enabled a further classification of patients according to their nutritional status: A, well nourished; B, moderately malnourished; and C, severely malnourished [6].

Weight and height were collected from the medical records in order to calculate Body Mass Index (BMI). BMI was calculated using weight (kilograms) divided by height squared (meters) and classified according to World Health Organization as underweight, normal weight, overweight or obese. Triceps skinfold thickness (TST) and mid-arm muscle circumference (MAMC) were also measured, in order to evaluate fat and muscle loss, respectively [9].

2.3. Outcomes

CC was defined according to Fearon et al. [5], who classifies it as it follows: Precachexia, defined as <5% involuntary weight loss with other metabolic disturbance, such as anorexia; Cachexia, defined as >5% involuntary weight loss in the last 6 months or BMI <20 kg/m^2 in addition to ongoing weight loss of >2% or sarcopenia in addition to ongoing weight loss of >2%; Refractory Cachexia, defined as a patient unresponsive to treatment and with a life expectancy <3 months. Death records were collected in a 3-year period (from November 2012 to December 2015).

2.4. Statistical analysis

Statistical analysis was undertaken in SPSS software version 23.0 (SPSS for Windows, 2015). In descriptive analysis, results for numeric variables were expressed as means with standard deviation (SD) or median with interquartile range (IQR) and in absolute (n) and relative (%) frequency for categorical variables.

To evaluate the agreement between BMI vs PG-SGA, TST vs PG-SGA and MAMC x PG-SGA we used the Nonparametric test – Pearson's chi-square test of independence and a contingency table to analyze the independence between the classifications. For the continuous quantitative variables BMI, TST and MAMC, we performed the nonparametric Kruskal-Wallis test to compare their medians. ANOVA test was used to compare the means of BMI, TST and MAMC with PG-SGA classification.

To investigate if there was a dependent association between CC diagnosis according to Fearon criteria and death with PG-SGA classification, we used the Nonparametric test – Pearson's chi-square test of independence and a contingency table to analyze the independence between the classifications, combined with the nonparametric Kruskal-Wallis test, to compare their medians on their quantitative form.

Kaplan-Meier curve was used to analyze the survival rate difference between PG-SGA classification (A, B + C) and compared by the logrank test. We estimated the sensibility, specificity, positive predictive value (PPV) and negative predictive value (NPV) for PG-SGA ability to predict CC and death.

To investigate the possibility of new cutoff we applied the clustering technique, admitting 3 groups under Euclidean distance. Further, we used Analysis of Variance to compare the means of the formed groups, with the post hoc tests of Duncan and Scheffé.

3. Results

97 patients were enrolled in the study, which 50.5% (n = 49) were female and a median of age of 58 years old (IQR 48–65.5). Regarding the localization of the tumour, abdominal cancer (both upper and lower) was the most prevalent - 59.8% (n = 58). The BMI median was 25.22 kg/m^2 (IQR 21.81–29.47). Medians of PG-SGA, hospitalization time and overall survival were, 7 (2–12), 5 days (IQR 3–9) and 1120 days (139.5–1.120), respectively. Mostly of the patients (51.5%; n = 50) had a hospitalization time ≤ 5 days.

According to BMI measured at the hospital admission, 3.6% (n = 3) of the patients were classified as undernourished, while 52.3% (n = 44) were classified as overweight or obese. TST criteria, on the other side, classified 29.9% (n = 29) as moderate or severely malnourished. MAMC evaluation resulted in 49.5% (n = 48) with moderate or severe muscle depletion. Any stage of CC was present in 68% of the patients, according to Fearon criteria, with Pre-cachexia the most prevalent condition (Table 1).

PG-SGA classified almost half of the patients (49,5%; n = 48) as moderately malnourished (grade B) or as severely malnourished (grade C) and 50,5% (n = 49) as well nourished (grade A). Concerning the PG-SGA score, 80,4% (n = 78) of the patients indicated the necessity of some type of nutritional management, as it follows: 2–3 points, 14,4% (n = 14); 4–8 points, 26,8% (n = 26); ≥9 points, 39,2% (n = 38) (Table 1).

There is a significant difference between the means of the PG-SGA score and the PG-SGA classification (p < 0.0001), with patients with severe malnourishment presenting the higher scores: A = 3.18; B = 11.12; C = 18.13.

Table 2 brings the comparison between PG-SGA and anthropometry. Median values for BMI and MAMC were significantly lower in patients classified as moderately malnourished compared to patients classified as well nourished. Regarding TST, all the 3 groups had significantly different values: patients in group A had the higher values, whereas patients in group C had the lower (p < 0.0001).

BMI, TST and MAMC inversely correlated with PG-SGA score, with r = −0.57, −0.51 and −0.47, respectively, and p < 0.0001. The higher the PG-SGA score, the lower is the values for the anthropometric measurements.

Significant associations were found between the classification categories of BMI, TST and MAMC and the classification of PG-SGA, as shown in Table 3. 70.3% (n = 26) of the patients classified as normal weight by BMI were moderately (B) or severely (C) malnourished, according to PG-SGA (p < 0.0001). As for TST, 92.3% (n = 12) of the patients with severe malnourishment according to fat mass were classified as B or C by PG-SGA (p < 0.0001). Nonetheless, 77.7% (n = 22) of the patients identified with muscle loss by MAMC were classified as B or C by PG-SGA (p < 0.0001).

There was a significant association between the categories of PG-SGA and the Fearon categories of CC. 80.6% (n = 25) of patients classified as well nourished (A) by PG-SGA showed no evidence of CC, whilst 60% (n = 9) of patients with severe malnourishment (C) were classified with refractory cachexia. A positive correlation between PG-SGA score and Fearon's categories of CC was also observed (r = 0.54; p < 0.0001).

Concerning death, the higher occurrence was observed in patients classified as severely malnourished (C) at the day of

Table 1
Clinical and anthropometric characteristics of the patients.

	n	%
Hospitalization time (days)		
≤5	50	51.5
>5	47	48.5
BMI at admission (kg/m^2)		
<18,5 (0)	3	3.6
18,5–24,9 (1)	37	44
25–29,9 (2)	27	32.1
≥30 (3)	17	20.2
TST percentile		
≤5	13	13.4
5–15	16	16.5
15–85	55	56.7
>85	13	13.4
MAMC percentile		
≤5	27	27.8
5–10	21	21.7
10–90	49	50.5
CC (Fearon criteria)		
No evidence of CC	31	32
Precachexia	28	28.8
Cachexia	23	23.7
Refractory cachexia	15	15.5
PG-SGA (Nutritional status)		
Well nourished (A)	49	50.5
Moderately malnourished (B)	33	34
Severely malnourished (C)	15	15.5
PG-SGA (Score)		
No need of nutritional intervention (0–1)	19	19.6
Might benefit from nutritional education (2–3)	14	14.4
Requires nutritional intervention (4–8)	26	26.8
Critical need of nutritional intervention (≥9)	38	39.2

BMI = Body Mass Index; TST = Triceps Skinfold Thickness; MAMC = Mid-arm Muscle Circumference; CC = Cancer Cachexia; PG-SGA = Patient-Generated Subjective Global Assessment.

Table 2
Comparison between the medians of anthropometric values according to PG-SGA classification.

PG-SGA	A		B		C		p*
	Median	IQR	Median	IQR	Median	IQR	
BMI	28,9	25.1–32.1	21.9	20.5–25.3	18.6	17.7–23.3	<0.0001
TST	75	50–85	25	15–50	10	5–10	<0.0001
MAMC	50	10–50	10	5–10	5	0–5	<0.0001

PG-SGA = Patient-Generated Subjective Global Assessment; IQR = Interquartile range; A = Well nourished; B = Moderately malnourished; C = Severely malnourished; BMI = Body Mass Index; TST = Triceps Skinfold Thickness; MAMC = Mid-arm Muscle Circumference. *Kruskal-Wallis test with significance at p < 0.05. ANOVA and Duncan tests.

Table 3
Association between the classification categories of BMI, TST and MAMC and the classification of PG-SGA.

	PG-SGA			Total	X^2	P
	A	B	C			
	n	n	n			
BMI (kg/m^2)						
0 (<18.5)	0	1	2	3	33.464	<0.0001
1 (≥18.5–24.9)	11	20	6	37		
2 (25–29.9)	19	7	1	27		
3 (≥30)	16	1	0	17		
Total	**46**	**29**	**9**	**84**		
TST (mm)						
0 (<5)	1	5	7	13	31.509	<0.0001
1 (5–15)	4	7	5	16		
2 (15–85)	34	18	3	55		
3 (>85)	10	3	0	13		
Total	**49**	**33**	**15**	**97**		
MAMC (mm)						
0 (≤5)	6	10	11	27	29.939	<0.0001
1 (>5 e ≥ 10)	8	12	1	21		
2 (>10 e ≤ 90)	35	11	3	49		
Total	**49**	**33**	**15**	**97**		

BMI = Body Mass Index; TST = Triceps Skinfold Thickness; MAMC = Mid-arm Muscle Circumference; PG-SGA = Patient-Generated Subjective Global Assessment; A = Well nourished; B = Moderately malnourished; C = Severely malnourished.

Table 4
Association between PG-SGA classification and Fearon's categories of CC.

Fearon's classification of CC	PG-SGA			Total	X^2	P
	A	B	C			
	n	N	n			
No evidence of CC	25	4	2	31	42.978	<0.0001
Precachexia	15	11	2	28		
Cachexia	8	13	2	23		
Refractory cachexia	1	5	9	15		
Total	49	34	15	97		

PG-SGA = Patient-Generated Subjective Global Assessment; A = Well nourished; B = Moderately malnourished; C = Severely malnourished; CC = Cancer Cachexia; χ^2 = Pearson's chi-square test.

hospitalization by PG-SGA (80%; n = 12), followed by the ones classified as moderately malnourished (B) (54.55%; n = 18). The patients classified as well nourished (A), though, had the lower rate of death (24.5%; n = 12). The association between PG-SGA categories and death occurrence was significant, with χ^2 = 16,991 e p < 0.0001 (Tables 4 and 5).

Figures 1 and 2 demonstrate that the risk of death elevates according to the classification of PG-SGA. Statistic logrank value was 17.533, with 2 degrees of freedom and p < 0.0001. These data indicate a significant statistical difference among the categories of PG-SGA classification. In survival curves, it was observed that patients with severe malnourishment (C) had the lowest survival time. The association of PG-SGA categories and hospitalization time did not differ statistically (p = 0.0705).

As for the outcomes CC and death, the PG-SGA demonstrated good sensibility (87.50%) and accuracy (72%) for CC, in addition to good specificity (75.51%) and accuracy (69%) for death (Table 6).

4. Discussion

CC is a condition that predisposes cancer patients to poorer prognosis and can ultimately lead to death [4]. Although CC is high prevalent and its effects are quite understood at the moment, there are challenges to its diagnosis on the daily clinical practice. As pointed out by Ryan et al. [3], malnutrition, cachexia and sarcopenia are "the skeleton in the hospital closet" for the last 40 years. As long as the current scientific knowledge about these consumptive disorders allows us to recognize it as an important factor contributing to high death risk in cancer patients, the evidences since its discovery reveal that we did not advance on the diagnosis and treatment of CC as much as was expected.

Regarding the diagnosis, for decades there was no consensus about the ideal parameters to consider that the patient developed CC. This question was appeased only in 2011, by Fearon et al. [5]. The authors published an international consensus with cutoffs to classify and diagnose cachexia in patients with cancer, with focus on involuntary weight loss: Precachexia, defined as <5%

Table 5
Association between PG-SGA classification at hospital admission and death occurrence.

Death	PG-SGA			Total	X^2	P
	A	B	C			
	n	N	n			
No	37	15	3	55	16.991	<0.0001
Yes	12	18	12	42		
Total	49	33	15	97		

PG-SGA = Patient-Generated Subjective Global Assessment; A = Well nourished; B = Moderately malnourished; C = Severely malnourished; χ^2 = Pearson's chi-square test.

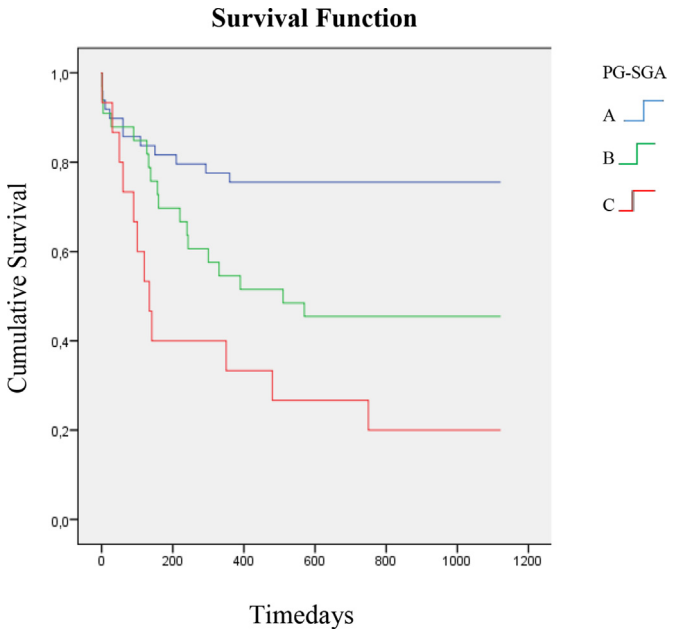

Fig. 1. Survival curve according to PG-SGA classification. PG-SGA = Patient-Generated Subjective Global Assessment; A (blue) = Well nourished; B (green) = Moderately malnourished; C (red) = Severely malnourished.

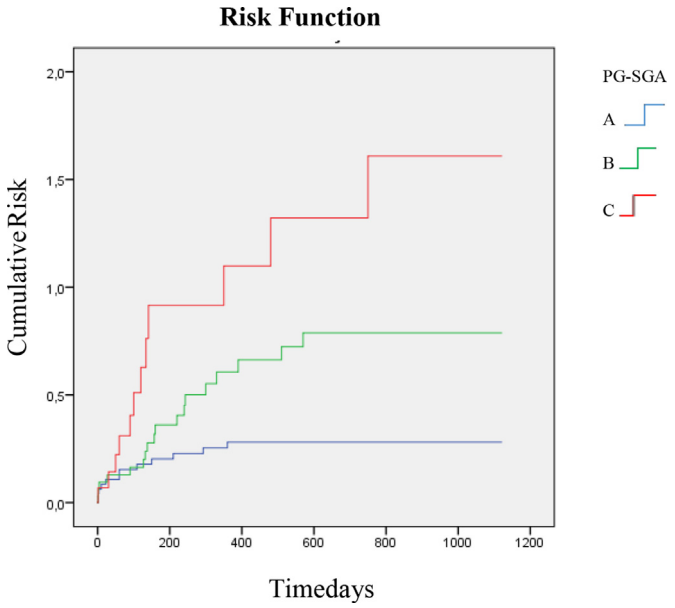

Fig. 2. Death risk curve according to PG-SGA classification. PG-SGA = Patient-Generated Subjective Global Assessment; A (blue) = Well nourished; B (green) = Moderately malnourished; C (red) = Severely malnourished.

Table 6
Sensibility, specificity, PPV e NPV of PG-SGA in the prediction of CC and death.

Outcomes (%)	SE	SP	PPV	NPV	Accurácy
CC	87.5	51.02	63.64	80.65	72[a]
Death	62.5	75.51	71.43	67.27	69[a]

PG-SGA = Patient-Generated Subjective Global Assessment; CC = Cancer Cachexia; SE = Sensibility; SP = Specificity; PPV = Positive Predictive Value; NPV = Negative Predictive Value.
[a] Confidence interval = 95%.

involuntary weight loss with other metabolic disturbance, such as anorexia; Cachexia, defined as >5% involuntary weight loss in the last 6 months or BMI <20 kg/m^2 in addition to ongoing weight loss of >2% or sarcopenia in addition to ongoing weight loss of >2%; Refractory Cachexia, defined as a patient unresponsive to treatment and with a life expectancy <3 months.

Interestingly, the authors introduced subclasses to CC, such as Precachexia and Refractory Cachexia. Some authors discuss whether or not this subclassification has clinical utility, specially between patients with no CC and patients with Precachexia [4,10]. Although there is still room for discussion concerning CC diagnostic criteria, the consensus proposed by Fearon certainly guided both clinical practice and research about this syndrome.

Head and neck cancer are specially related to poor nutritional status, with data showing that about half of these patients suffer from malnutrition and about 80% present unintentional weight loss throughout the treatment [11,12]. According to the United Kingdom National Multidisciplinary Guidelines of 2016 [13], malnutrition in these patients is associated with several life-threatening signs and symptoms, such as increased risk of infection, impaired cardiac function, increased risk of post-operative complications and reduced response to chemotherapy and radiotherapy.

Abdominal cancer is a category that encompasses several types of cancer, such as esophageal, gastric, pancreatic and others related to gastrointestinal system. According to Gala, Waitzberg & Tesser (2018) [14], this type of cancer is often related to malnutrition, cachexia syndrome, worsening of prognosis and shortened survival rate. That way, health professionals must investigate and screen head, neck and abdominal cancer patients for CC.

In our study, 68% (n = 60) of the patients developed some grade of CC. It was expected, since the prevalence of CC in cancer patients can reach up to 80% [1–5]. When we tested the association between PG-SGA classification, anthropometry and CC, only PG-SGA showed a positive correlation with CC with statistical significance, while anthropometry did not (data not shown). The possible explanation for this is that PG-SGA, an ease to use nutritional screening tool, is recommended for routine utilization in hospital, especially in cancer patients. It is well stablished in clinical practice, with authors suggesting it is a "4-in-1" instrument: PG-SGA virtually may be used to screening, assessment, triage and monitoring the nutritional status of patients [6]. Evidence shows that it is useful even in patients with advanced cancer in palliative care [15].

Another reason may be that PG-SGA is a broad questionnaire, involving unwanted weight-loss, dietary intake, gastrointestinal disturbances and clinical exam, while both TST and MAMC relies on a single-compartment percentiles classification. We hypothesize that some patients may be obese and present Precachexia or Cachexia, with recent unwanted weight-loss, but because of the initial high weight, may decrease both muscle mass and fat and still be classified on percentiles regarded as adequate. This hypothesis is special relevant given that obesity rates are increasing worldwide [16–18], and obesity is directly related to several types of cancer [19–21].

Although PG-SGA is recognized as an instrument useful for the hospital routine in cancer patients, no study had yet evaluated the association between PG-SGA performance with the prediction of CC. Our study was able to show that PG-SGA classification predicted CC and was even associated with the class of CC: proportionally, patients classified as A in PG-SGA presented no CC or precachexia; patients classified as B presented more cachexia; and patients classified as C presented more refractory cachexia. That way, the higher the degree of malnourishment according to PG-SGA, higher the severity of CC.

Since malnutrition is often related to risk of death in cancer patients [22], we also evaluated the association between PG-SGA performance and survival along three years. Our study evidenced a higher rate of death in patients classified as C the day of the hospital admission. The Kaplan-Meier curves revealed an ascending cumulative risk of death for patients classified as A, B or C, respectively. Compared to A, C patients presented almost 1.5 times higher risk of dying in the 3 years of the study. This result elicits a tendency of death observed in patients screened by PG-SGA (especially graded C), therefore it suggests that the clinical intervention must be made at the time of the PG-SGA application.

A limitation of our study is that, due to the number of patients recruited, we could not analyze whether head and neck cancer patients had different results compared to abdominal cancer patients. However, as we previously showed in a nationwide multicentric study conducted in Brazil [23], upper digestive cancer and head and neck cancer are two of the most malnutrition-related cancers in our population, with identical odds ratio and confidence interval for malnutrition. The main finding of our study is that we analyzed PG-SGA upon hospital admission and evaluated patient outcomes for about 3 years.

Our data suggest that PG-SGA is a useful tool for the prediction of both CC and death in head, neck and abdominal cancer, with good sensibility, specificity and accuracy. In order to further investigate this association, additional future follow-up studies are necessary.

Conflict of interest statement

The authors declare no conflict of interest.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Fabiana Felix Cavalcante Martins: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft. **Nivaldo Barroso de Pinho:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft. **Patrícia de Carvalho Padilha:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - review & editing. **Renata Brum Martucci:** Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing - review & editing. **Viviane Dias Rodrigues:** Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing - review & editing. **Rafael Carvalho Sales:** Data curation, Formal analysis, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Wilza Arantes Ferreira Peres:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - review & editing.

Acknowledgements

The authors would like to thank the nutrition staff of INCA for the support for this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.03.013.

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